

## **REMARKS**

### **Status of the claims**

Claims 15-64 are pending in the application, and have been examined.

In the present Office action, claims 25-34 and 45-64 are rejected for alleged lack of enablement, claims 15-22, 25-32, 35-42, 45-52, and 55-62 are rejected allegedly for failing to comply with the written description requirement, and claims 15- 54 are rejected allegedly for being obvious.

By this amendment, claims 15-33, 35-43, and 45-63 have been cancelled and the remaining pending claims amended. In addition, new claims 65 – 69 have been added. Thus, after entry of this amendment, claims 34, 44, 64, and 65 – 69 are pending in the application.

### **Amendments to the Claims**

Claims 34, 44, and 64 have been amended to become independent claims. In addition, in claims 34 and 44 the phrase “wherein the patient does not have cancer” has been added. The addition of this phrase is supported by the specification as filed (see, for example, paragraphs [0153] and [0154]).

New claim 65 is drawn to a method of treating osteoporosis. Support for this claim can be found in the specification as filed, for example in paragraph [0153].

New claims 66 - 69 each recites the single compound 5-(5-fluoro-2-oxo-1,2-dihydro-indolin-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (Compound 1) or a salt thereof. Support for these claims can be found in the specification as filed, for example in the Examples and claims. Neither of the amendments adds new matter.

The cancellation of and amendments to the claims are solely for the purpose of expediting the allowance of the application and not for patentability reasons. Applicant respectfully requests the entry and consideration of the amendments.

### **Rejection of Claims 25-34 and 45-54 under 35 USC § 112, First paragraph**

Claims 25-34 and 45-54 are rejected under 35 USC § 112, first paragraph, allegedly failing to comply with the enablement requirement.

Applicants by this amendment have cancelled claims 25-33 and 45-54, which renderw the rejection thereto moot.

Claim 34 is drawn to a method of treating excessive osteolysis in a patient having cancer that has metastasized to bone. New claim 67, which depends from claim 34, recites a single compound, which is “Compound 1” identified in the specification and in the Office action. The Examiner has acknowledged that the use of Compound 1 is enabled. (page 4 of the office Action); Therefore, the rejection does not apply to claim 67. Applicants respectfully traverse the basis of rejection to claim 34 for the reasons below.

The Examiner explained her basis of rejection by discussing a number of Wands’ factors. Specifically, regarding the “Nature of the Invention,” the Examiner alleges that “the skilled artisan would not be able to determine “what is defined by excessive osteolysis” and questions “At what point is osteolysis excessive?” Applicants believe, however, that a skilled artisan would not be able to readily determine “what is defined by excessive osteolysis” and that the specification has clearly disclosed at what point osteolysis is excessive. First, the Examiner has already acknowledged that use of Compound 1 for treating excessive osteolysis is enabled. (page 4 of the office Action), to which Applicants fully agree. This indicates that the Examiner is convinced that a skilled artisan would be able to determine “what is defined by excessive osteolysis” and to determine “at what point is osteolysis excessive” and is able to practice the claims invention without undue experimentation.

Further, Applicants respectfully submit that the term “Excessive osteolysis,” which is a term of art known to those skilled in the art, is clearly defined in the specification. In this regard, Applicants wish to draw the Examiner’s attention to the specification, particularly paragraph [0054], where it provides:

“Excessive osteolysis” refers to an imbalance between osteolytic and osteogenic activities that results in net loss of bone, either locally or systemically.

(see bottom of paragraph [0054], emphasis added)

This definition is clear to a person skilled in the art. It clearly discloses that osteolysis is excessive when there is a net loss of bone. The definition further teaches that excessive osteolysis can be determined by measuring loss of bone. Loss of bone is routinely measured and treated in the field of medical art. Accordingly, Applicants respectfully submit that a skilled artisan would be able to determine what is defined by excessive osteolysis without undue experimentation.

With respect to the “Breadth of the Claims,” the Examiner alleges that the claims encompass treating many pathologies characterized by excessive osteolysis without defining what these osteolytic diseases entail. As disclosed in paragraph [0153] of the specification, it is true that osteoporosis and excessive osteolysis may be attributed to different underlying conditions or disorders, such as aging, menopause, and eating disorders; however, the claimed invention is not drawn to a method of treating these underlying conditions or disorders. Rather, it is drawn to a method of treating the single condition of excessive osteolysis. As discussed above, the specification discloses that “excessive osteolysis” involves an imbalance between osteolytic and osteogenic activities that results in net loss of bone and that osteoclasts are a primary example of cells that cause osteolysis. Applicants have found that compounds having structure of formula I and formula II inhibit the development of osteoclast and thus useful for treating excessive osteolysis. (See specification, paragraph [0053]). Thus, defining the underlying causes for excessive osteolysis is not required for practicing the claimed invention.

Regarding the “Predictability of the Art,” the Examiner alleges that claimed invention is unpredictable in terms of identifying diseases that are characterized by excessive osteolysis. Applicants respectfully disagree and wish to reiterate the reasons provided above.

Regarding the level of the skill in the art, the Examiner states that the level is high and that “one of skill in the art must perform exhaustive search to determine which diseases are associated with excessive osteolysis and what compounds of the instant claims are to practice the claimed invention. Applicants respectfully submit that a high level of skill in the art favors a finding of enablement. Applicants further submit that, as indicated above, practicing the invention does not require determining which diseases are associated with excessive osteolysis. Further, claim 34 recites only 9 compounds, one of which the Examiner has acknowledged to

be enabled; therefore, contrary to the Examiner's assertion, a person skilled in the art will not be required to "perform exhaustive search" to determine which compounds may be used.

With respect to the "Amount of Experimentation Necessary," the Examiner alleges that to practice the invention one of skill in the art would have to first determine at what point osteolysis becomes excessive as well as dosages, duration of treatment and route of administration and to determine appropriate animal model to determine whether or not a compound is effective. Applicants submit diagnosis of diseases, including bone diseases, as well determination of treatment regimen, is merely routine for persons skilled in the art. Examiner also alleges that to practice the invention one of skill in the art would have to determine appropriate animal model to determine whether or not a compound is effective. Applicants submit that appropriate animal models for testing a compound's effect on excessive osteolysis and methods of testing are known, available, and routinely practiced in the art. Further, the 9 compounds recited in claim 34 share an active core structure and have close overall structural similarities. The specification in Example 8 discloses experimental data with one of these compounds showing its property in inhibiting the development of osteoclast, a major cell type that causes osteolysis, which suggests the compound's usefulness for treating excessive osteolysis. Because of the structural similarity a person skilled in the art would reasonably expect them to have similar property of inhibiting development of osteoclast. If any experimentation is ever needed, it is merely routine and can be easily performed according to the guidance provided in the specification and what is known in the art. Therefore, there would be no undue experimentation. "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F. 2d at 737, 8 USPQ 2d at 1404 (1982).

**Rejection of Claims 55-64 under 35 USC § 112, first paragraph:**

Claims 55-64 are also rejected under 35 USC § 112, first paragraph, allegedly for failing to comply with the enablement requirement. Claims 55-63 have been cancelled by this amendment, which renders the rejection thereto moot. The remaining claim 64 is drawn to a method of treating excessive osteolysis in a patient that is post-menopausal and recites 9 specific compounds. New claim 69, which depends from claim 64, recites a single compound

(i.e., Compound 1). The Examiner has acknowledged that the use of compound 1 is enabled; therefore, the rejection does not apply to claim 69.

The Examiner's alleged basis for the rejection here is essentially the same as that for the rejection of claims 25-34 and 45-54. Applicants respectfully traverse the rejection and to reiterate the reasons provided above in addressing the rejection to claims 25-34 and 45-54.

**Rejection under 35 USC § 112, first paragraph (Regarding Written Description):**

Claims 15-22, 25-32, 35-42, 45-52, and 55-62 are rejected under 35 USC 112, first paragraph, allegedly as failing to comply with the written description requirement. The claims at issue have been cancelled by the present amendment; accordingly the rejection is mooted.

**Rejection under 35 USC § 103**

The office action states that claims 15-34 and 35-54 are rejected under 35 USC 103 (a) as being unpatentable over Mendel et al., Clinical Cancer Research, vol. 9, 327-337, 2003 in view of Tang et al. US 6,573,293. Among these claims, claims 15-33, 35-43, and 45-54 have been cancelled by this amendment, which renders the rejection thereto moot, while claims 34 and 44 pending.

Claim 34 is drawn to a method of treating excessive osteolysis in a patient having cancer that has metastasized to bone and recites 9 specific compounds. New claim 67, which depends from claim 34, recites a single compound. In making the rejection the Examiner alleges that it would have been obvious to one of ordinary skill in the art to use the disclosed compounds for inhibition of phosphorylation and treatment of osteolysis in a patient with cancer. Claim 34 has been amended to include the recitation "wherein the patient does not have cancer." Neither of the cited references teach or suggests, nor does the Examiner allege, that use of the recited compounds for treating excessive osteolysis in a patient who does not have cancer. Accordingly, claims 34 and 67 would not have been obvious to a person skilled in the art.

Claim 44 and new claim 68, which depends from claim 44, are drawn to a method of treating excessive osteolysis in a patient that has osteoporosis. In finding the claims invention

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are prima facie obvious, the Examiner states that “treating cancer will effectively treat or inhibit bone osteolysis.” Without conceding the correctness of the examiner’s assertion and for the sole purpose of expediting the allowance of the application, claim 44 has been amended to include the recitation “wherein the patient does not have cancer.” New claim 68 also include this recitation. In addition, new claims 44, 65, and 66 also includes this phrase. Applicants submit that the cited references does not teach or suggest the use of the cited compounds for treating a patient that does not have cancer patients, nor does the Examiner allege it does; therefore, the subject matter of claims 44 and 65 would not have been obvious to a person skilled in the art.

In light of the amendments and comments above, Applicants respectfully request the withdrawal of the rejections and the issuance of a notice of allowance.

Respectfully submitted,

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